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ORIGINAL RESEARCH ARTICLE

Effect of Colchicine on Coronary Plaque Stability in Acute Coronary Syndrome as Assessed by Optical Coherence Tomography: The COLOCT Randomized Clinical Trial

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BACKGROUND: Colchicine has been approved to reduce cardiovascular risk in patients with coronary heart disease on the basis of its potential benefits demonstrated in the COLCOT (Colchicine Cardiovascular Outcomes Trial) and LoDoCo2 (Low-Dose Colchicine 2) studies. Nevertheless, there are limited data available about the specific impact of colchicine on coronary plaques.

METHODS: This was a prospective, single-center, randomized, double-blind clinical trial. From May 3, 2021, until August 31, 2022, a total of 128 patients with acute coronary syndrome aged 18 to 80 years with lipid-rich plaque (lipid pool arc >90°) detected by optical coherence tomography were included. The subjects were randomly assigned in a 1:1 ratio to receive either colchicine (0.5 mg once daily) or placebo for 12 months. The primary end point was the change in the minimal fibrous cap thickness from baseline to the 12-month follow-up.

RESULTS: Among 128 patients, 52 in the colchicine group and 52 in the placebo group completed the study. The mean age of the 128 patients was 58.0±9.8 years, and 25.0% were female. Compared with placebo, colchicine therapy significantly increased the minimal fibrous cap thickness (51.9 [95% CI, 32.8 to 71.0] μm versus 87.2 [95% CI, 69.9 to 104.5] μm; difference, 34.2 [95% CI, 9.7 to 58.6] μm; *P*=0.006), and reduced average lipid arc (−25.2° [95% CI, −30.6° to −19.9°] versus −35.7° [95% CI, −40.5° to −30.8°]; difference, −10.5° [95% CI, −17.7° to −3.4°]; *P*=0.004), mean angular extension of macrophages (−8.9° [95% CI, −13.3° to −4.6°] versus −14.0° [95% CI, −18.0° to −10.0°]; difference, −6.0° [95% CI, −11.8° to −0.2°]; *P*=0.044), high-sensitivity C-reactive protein level (geometric mean ratio, 0.6 [95% CI, 0.4 to 1.0] versus 0.3 [95% CI, 0.2 to 0.5]; difference, 0.5 [95% CI, 0.3 to 1.0]; *P*=0.046), interleukin-6 level (geometric mean ratio, 0.8 [95% CI, 0.6 to 1.1] versus 0.5 [95% CI, 0.4 to 0.7]; difference, 0.6 [95% CI, 0.4 to 0.9]; *P*=0.025), and myeloperoxidase level (geometric mean ratio, 1.0 [95% CI, 0.8 to 1.2] versus 0.8 [95% CI, 0.7 to 0.9]; difference, 0.8 [95% CI, 0.6 to 1.0]; *P*=0.047).

CONCLUSIONS: Our findings suggested that colchicine resulted in favorable effects on coronary plaque stabilization at optical coherence tomography in patients with acute coronary syndrome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04848857.

Key Words: acute coronary syndromes ■ colchicine ■ inflammation ■ optical coherence tomography

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.124.069808.
For Sources of Funding and Disclosures, see page 992.
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Clinical Perspective

What Is New?

- This study first demonstrated that addition of colchicine to standard medical therapy significantly improved plaque stability in acute coronary syndrome as assessed by optical coherence tomography.
- This study shed light on the effect of colchicine on plaque stability improvement through the vascular inflammation inhibition.

What Are the Clinical Implications?

- This study provided the mechanistic rationale in favor of colchicine reducing recurrent atherothrombotic events in acute coronary syndrome.
- This study was helpful for the interpretation of the cardiovascular outcomes trials associated with colchicine.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AZU1	azurocidin 1
CHD	coronary heart disease
COLCOT	Colchicine Cardiovascular Outcomes Trial
COLOCT	Colchicine–Optical Coherence Tomography Trial
CONSORT	Consolidated Standards of Reporting Trials
FCT	fibrous cap thickness
GMR	geometric mean ratio
hsCRP	high-sensitivity C-reactive protein
IL	interleukin
IL-1RA	IL-1 receptor antagonist
LDL-C	low-density lipoprotein cholesterol
MPO	myeloperoxidase
NLRP3	NOD-like receptor family pyrin domain containing 3
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PCSK9i	proprotein convertase subtilisin/kexin-9 inhibitors
TCFA	thin-cap fibroatheroma

Coronary heart disease (CHD) is the leading cause of mortality and rising health care costs worldwide.[1,2] Inflammation is independently associated with the progression of CHD, including inciting plaque instability and inducing acute coronary syndrome (ACS).[3–5] Successful therapy targeting inflammation in patients with CHD is challenging.[6] Until recently, 3 major randomized clinical trials (CANTOS [Canakinumab Anti-Inflammatory Thrombosis Outcome Study], COLCOT [Colchicine Cardiovascular Outcomes Trial], and LoDoCo2 [Low-Dose Colchicine 2]) have demonstrated that targeting inflammation through inhibition of the NLRP3 (NOD-like receptor family pyrin domain containing 3)–IL (interleukin)-1β–IL-6 pathway significantly reduces cardiovascular events with an acceptable safety profile.[7–10]

Colchicine is recommended for the therapy of gout and pericarditis because of its broad anti-inflammatory action.[11] The US Food and Drug Administration and Health Canada recently approved colchicine to reduce cardiovascular risk in adult patients with CHD on the basis of the potential clinical benefit of colchicine in the COLCOT and LoDoCo2 studies.[10,12] Nevertheless, few studies have directly clarified the effect of colchicine on atherosclerotic plaque. To date, only 1 nonrandomized study has revealed that colchicine favorably modifies coronary plaque by reducing the low attenuation plaque volume in 80 patients with ACS, as assessed by coronary computed tomography angiography.[13]

Intravascular optical coherence tomography (OCT) is a high-resolution imaging technique for evaluating coronary plaque characterization. High-risk plaque features on OCT such as thin-cap fibroatheroma (TCFA) and large necrotic core can predict increased risk for future adverse cardiac events.[14,15] Currently, OCT is widely used to evaluate the modulation of atherosclerotic plaque in response to different therapies.[16,17] Thus, we conducted COLOCT (Colchicine–Optical Coherence Tomography Trial) to explore the effects of colchicine on coronary plaque characterization by OCT.

METHODS

The authors declare that all supporting data are available within the article and its Supplemental Material.

Study Design

This was an investigator-initiated, prospective, single-center, randomized, double-blind, placebo-controlled clinical trial conducted at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology in China.

The trial protocol was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology ([2020]0162-01) and registered in the clinicaltrial.gov registry (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04848857). All procedures in this study were conducted in accordance with the principles of Good Clinical Practice and the guidelines of the Declaration of Helsinki. All patients provided written informed consent. This study was reported according to the CONSORT guidelines (Consolidated Standards of Reporting Trials).[18]

Study Population

Eligible patients were enrolled according to the following inclusion criteria: (1) men or women ≥18 and ≤80 years of age,

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capable and willing to provide informed consent; (2) hospitalized patients diagnosed with ACS within 1 month; (3) at least 1 nonculprit lesion with a diameter stenosis percentage of 30% to 70% by visual estimation on coronary angiography after completing any planned percutaneous revascularization; and (4) the lesion was shown by OCT to be a lipid-rich plaque (lipid pool arc >90°).

The main exclusion criteria were as follows: (1) allergy to colchicine; (2) taking colchicine within 10 days before randomization; (3) abnormal liver function (alanine aminotransferase >3 times the upper limit of normal value); (4) abnormal renal function (creatinine clearance rate <45 mL/min); (5) thrombocytopenia (platelet count <100 G/L); (6) uncontrolled infectious diseases; (7) known immune diseases or immune-related diseases such as systemic lupus erythematosus, asthma, inflammatory bowel disease, gout, malignant tumor, etc; (8) pre-existing or plan for the administration of systemic anti-inflammatory treatments such as nonsteroidal anti-inflammatory drugs, hormones, and immunomodulatory and chemotherapeutic drugs; (9) a history of surgery or interventional therapy in the past 6 months; (10) a history of coronary artery bypass grafting or a plan for coronary artery bypass grafting within 1 year; (11) left main coronary disease (≥50% reduction in lumen diameter by angiographic visual estimation); (12) significant coronary calcification or tortuosity deemed to preclude OCT evaluation; (13) mental disorders such as anxiety or depression; (14) pregnant women, lactating women, or women of childbearing age not using effective contraceptive methods; (15) participation in other clinical trials in the past 3 months; (16) not receiving standardized treatment after being diagnosed with CHD; (17) estimated life expectancy less than 1 year; and (18) unsuitability for this trial, as judged by the researchers.

Randomization and Interventions

Randomization was performed once eligibility was confirmed, written informed consent was obtained, and the baseline imaging procedure was successfully completed. Participants were randomly allocated according to a simple randomization procedure (computer-generated list of random numbers performed by statistical experts) to different treatment groups. The medications were prepacked in bottles and consecutively numbered for each participant following the randomization schedule. The allocation sequence was concealed in sequentially numbered, opaque, sealed and stapled envelopes. Before randomization, study medication numbers were assigned to the participants. All treatment packs were identical and contained either colchicine (manufactured by Banna Pharmaceutical Co Ltd, China) or placebo that was matched to colchicine for taste, color, and size and contained starch in a white circular tablet. The details of the series were unknown to any of the investigators or to the coordinator. The investigators, participants, treating physicians, outcome assessors, and data analysts were all blinded to treatment allocation.

All subjects were treated with currently recommended therapies after ACS according to the national guidelines. We assigned patients in a 1:1 ratio to receive 1 tablet of colchicine (0.5 mg) or placebo, administered orally daily for 12 months. During the treatment period, patients underwent on-site visits at months 1 and 12, and phone visits at months 3 and 6. Counts of pills in the medication bottles returned by the participants were used for adherence monitoring. Serial imaging of the target coronary plaque was performed by OCT at baseline and repeated at the 12-month follow-up. The final end of study visit was conducted at 12 months to complete the safety assessment.

Imaging Acquisition, Definition, and Analysis

OCT imaging was performed and acquired using a frequency-domain OCT system (ILUMIEN OPTIS Mobile, Abbott Vascular). After administration of intracoronary nitroglycerin, motorized pullback OCT imaging at a speed of 36 mm/s for a total of 75 mm was performed using a 2.7F Dragonfly OPTIS imaging catheter (Abbott Vascular). During the OCT pullback, blood was cleared from the vessel by injecting contrast agent. Angio coregistration was performed with the OPTIS integrated system to coregister the angiogram and the OCT image. After interventional treatment for all culprit lesions, OCT identified nonculprit lesions as the untreated coronary artery segments with luminal stenosis and a loss of the normal vessel wall architecture. The nonculprit lesion had a diameter stenosis percentage of 30% to 70% by visual estimation on coronary angiography and a lipid pool arc >90°, which was located >10 mm from the percutaneous coronary intervention (PCI)–treated lesion. In the case of multiple nonculprit lesions eligible for OCT imaging, the imaging of each nonculprit lesion was performed in all the 3 main epicardial coronary arteries (the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery). A distance of >5 mm on the longitudinal view was considered as 2 separated nonculprit lesions. The conditions of coronary angiography and OCT were consistent at baseline and follow-up, including the same position, equipment, etc.

All imaging performed was anonymized, digitally stored, and sent to the Intravascular Imaging and Physiology Core Laboratory of the Second Affiliated Hospital of Harbin Medical University (iMcorLab, Harbin, China) for analysis. Paired baseline and follow-up OCT images were analyzed using a dedicated offline review system (Abbott Vascular). The segment was selected between 2 anatomical landmarks (distal: side branches; proximal: left-main bifurcation/ostium or side branches close to the ostium of the right coronary artery). The same segment was measured by 2 independent analysts who were blinded to the clinical presentation and patient characteristics (C.Z. and H.-B.J.). All of the OCT analyses were performed every 1 mm along the entire plaque. For each image with plaque, the minimum fibrous cap thickness (FCT), lipid arc, macrophage infiltration, presence of TCFA, minimum lumen area, calcification, cholesterol crystal, and microvessels were recorded. The definitions of these OCT parameters were derived from the published expert consensus.[19–22] Briefly, fibrous cap was defined as a signal-rich homogeneous band overlying a lipid core. The calculation of minimal FCT was obtained by measuring the FCT at the thinnest site. The measurement of lipid arc was conducted within lipid-rich plaques, and the maximum and mean values were recorded. Macrophage infiltration was defined as bright spots with signal-rich, distinct, or confluent punctate regions accompanied by heterogeneous backward shadows. The angular extension of macrophages was measured in degrees.[17] TCFA was defined as a lipid plaque in which the minimum FCT was <65 μm and lipid arc >90° in circumference. The minimum lumen area was automatically measured and manually corrected if necessary. Calcified plaque exhibited signal-poor regions with sharply delineated borders and limited shadowing. Cholesterol crystal was defined as a thin linear

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regions of high intensity. Microvessels appeared in OCT as signal-poor voids that were sharply delineated and usually followed in multiple contiguous frames. The intraclass correlation coefficient for the repeated FCT measurements by the same observer was 0.939. The intraclass correlation coefficient for measuring FCT by 2 different observers was 0.907.

Sample Collection and Laboratory Assessment

Blood samples were obtained in the morning after overnight fasting at baseline (on admission) and 12 months during the follow-up. Clinical laboratory testing was performed using commercial kits in the Department of Clinical Laboratory in Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, according to the clinical care needs of the patient.

Levels of hsCRP (high-sensitivity C-reactive protein) were measured using the CardioPhase hsCRP assay (Siemens Healthcare Diagnostics, Germany). The plasma protein levels of IL-1RA (IL-1 receptor antagonist, Neobioscience, China), IL-6 (Neobioscience, China), IL-18 (Neobioscience, China), myeloperoxidase (MPO, Neobioscience, China), and azurocidin 1 (AZU1, Reed Biotech, China) were detected by enzyme-linked immunosorbent assay kits according to the manufacturer's instructions.

Outcomes

The primary end point was the change in the minimal FCT from baseline to the 12-month follow-up. The secondary end points include the following: (1) change in the average lipid arc; (2) change in macrophage accumulation (mean angular extension of macrophages); (3) change in the incidence of TCFA; (4) change in minimum lumen area; (5) change in levels of inflammatory biomarkers (hsCRP, IL-6, and MPO); and (6) major adverse cardiovascular and cerebrovascular events defined as the composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and revascularization because of ischemia. All serious adverse events were recorded. Other recorded adverse events included those related to colchicine or placebo, as well as the laboratory abnormalities with clinical significance determined by the investigator. All clinical end points were adjudicated independently by the clinical end point committee, consisting of experienced members who were blinded to the trial group assignments.

Study Sample Size

The sample size was calculated based on a previous study.[23] With an assumed change of 80±80 μm in FCT at the end of colchicine treatment, and an assumed change of 40±60 μm in the placebo group, the required sample size per group was determined to be 51 based on a 2-tailed α of 0.05, and a power of 0.8, using PASS 11. Considering an estimated dropout rate of 20%, the dropout-inflated sample size was calculated to be 128, with 64 in each group.

Statistical Analysis

Normally distributed continuous variables are expressed as the mean±SD, and nonnormally distributed continuous variables are expressed as median (first quartile, third quartile). Categorical variables are described as n (%). The analyses of normally distributed continuous variables for OCT were conducted on plaque level values at 2 time points (baseline and 12-month follow-up) using linear mixed model accounting for the multiple plaques per patient, by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and plaque identity as the random effect, adjusting for age. The analyses of categorical variables for OCT were conducted on plaque level values at 2 time points (baseline and 12-month follow-up) using generalized estimating equations for the multiple plaques per patient (plaque identity as subject variable, time point as within-subject variable, and the interaction between group and time point as factor of binary logistic model), adjusting for age. For the analyses of biochemical parameters and inflammatory biomarkers, the linear mixed model was conducted on patient-level values at 2 time points (baseline and 12-month follow-up) by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and patient identity as the random effect, adjusting for age. The nonnormally distributed variables were log-transformed to achieve the normality for the analysis of linear mixed model, and differences were expressed as geometric mean ratio (GMR, 95% CI). Spearman correlation analysis was used to explore the correlation between the percentage changes in OCT parameters and biochemical/inflammatory biomarkers. For the analysis of major clinical end points and adverse events, the chi-square or Fisher exact test was used as appropriate. All statistical tests were performed using SPSS26 or R Version 4.6.0.

RESULTS

Baseline Characteristics

From May 3, 2021, until August 31, 2022, a total of 128 patients were randomized to receive colchicine (n=64) or placebo (n=64) under the treatment of secondary prevention strategies according to the national guidelines. Among the 128 recruited patients, 52 patients in the placebo group and 52 patients in the colchicine group completed the study (Figure 1).

The baseline characteristics of the intention-to-treat population (n=128) are shown in Table 1. The mean age of the patients was 58.0±9.8 years (60.3±8.5 years in the placebo versus 55.7±10.6 years in the colchicine group; *P*=0.008), with 25.0% who were female, 25.0% with diabetes, 31.3% with previous CHD, and 10.9% with previous PCI. All patients in this hospitalization received treatment of PCI and medication (98.4% taking dual antiplatelet agent, 95.3% taking statins, 75.0% taking β-blockers, and 80.5% taking the renin angiotensin system inhibitors, respectively). The time from ACS to randomization was 12.1±7.7 days in 128 patients, 6.3% between days 0 and 3, 32.0% between days 4 and 7, and 61.7% at day 8 or after. The OCT target vessel numbers were 95 in the placebo group and 110 in the colchicine group. The OCT target plaque numbers were 138 in the placebo group and 167 in the colchicine group. There were no significant differences between the placebo and colchicine groups in terms

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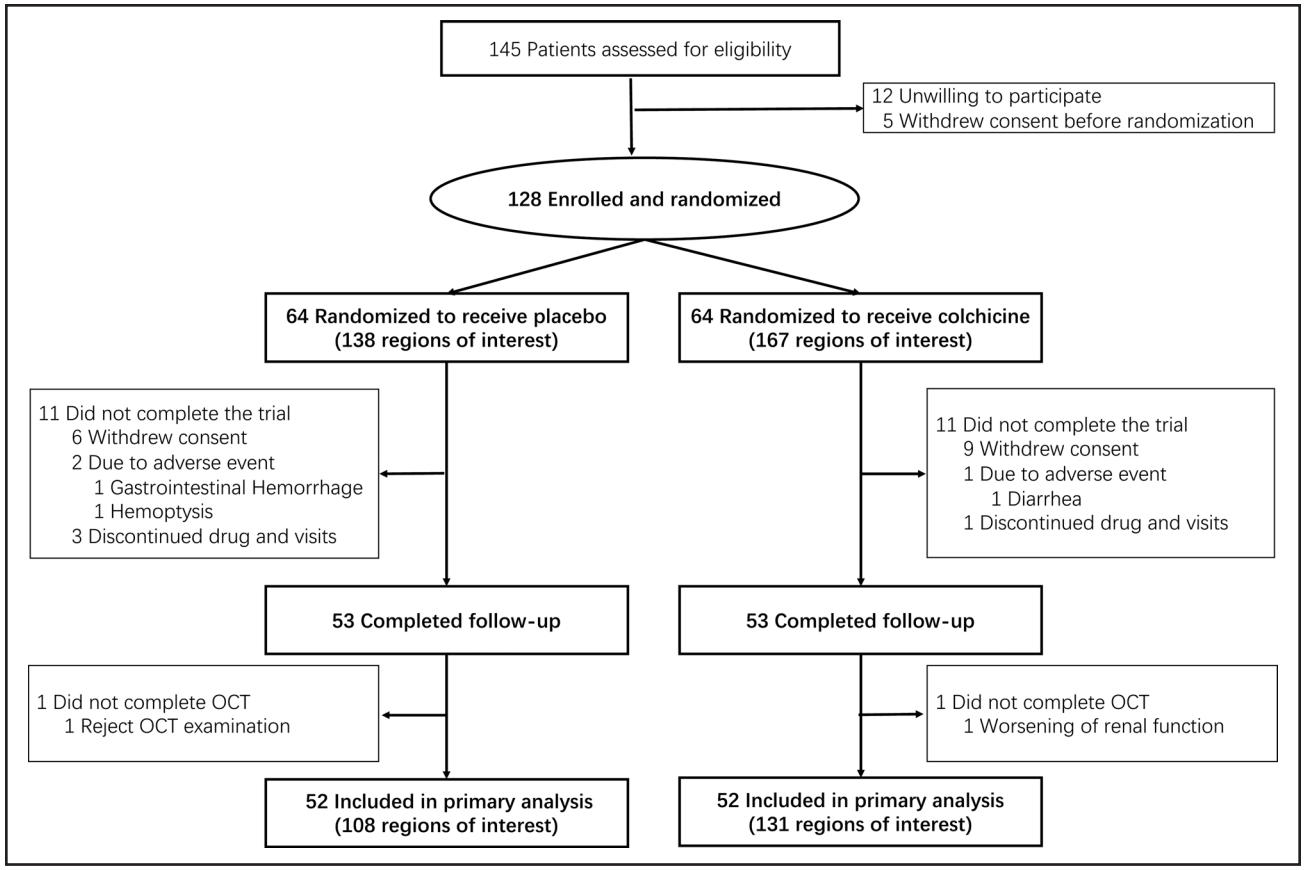
145 Patients assessed for eligibility
12 Unwilling to participate
5 Withdrew consent before randomization
128 Enrolled and randomized
64 Randomized to receive placebo
(138 regions of interest)
64 Randomized to receive colchicine
(167 regions of interest)
11 Did not complete the trial
6 Withdrew consent
2 Due to adverse event
1 Gastrointestinal Hemorrhage
1 Hemoptysis
3 Discontinued drug and visits
11 Did not complete the trial
9 Withdrew consent
1 Due to adverse event
1 Diarrhea
1 Discontinued drug and visits
53 Completed follow-up
53 Completed follow-up
1 Did not complete OCT
1 Reject OCT examination
1 Did not complete OCT
1 Worsening of renal function
52 Included in primary analysis
(108 regions of interest)
52 Included in primary analysis
(131 regions of interest)

Figure 1. Flow chart of the patients in this study.
OCT indicates optical coherence tomography.

of baseline data for sex, risk factors, previous history, type of ACS, time from ACS to randomization, distribution information of OCT target vessel, diameter stenosis percentage of the OCT target plaque, PCI performed information, and treatment. Although patients in the placebo group were older than those in the colchicine group, the proportion of patients over the age of 65 years between the 2 groups was not significantly different. The baseline characteristics of the per-protocol population (n=104) are shown in Table S1.

OCT Outcomes

The OCT parameters at baseline did not differ significantly between the placebo and colchicine groups (Table 2). Figure 2 showed the representative OCT images in patients at baseline and at the 12-month follow-up. The primary end point, the absolute value changes in minimal FCT levels after 12-month treatment, were 51.9 (95% CI, 32.8 to 71.0) μm for the placebo group, and 87.2 (95% CI, 69.9 to 104.5) μm for the colchicine group (difference, 34.2 [95% CI, 9.7 to 58.6]; *P*=0.006). Compared with the placebo group, colchicine therapy significantly influenced the change of the average lipid arc (−25.2° [95% CI, −30.6° to −19.9°] versus −35.7° [95% CI, −40.5° to −30.8°]; difference, −10.5° [95% CI, −17.7° to −3.4°]; *P*=0.004) and mean angular extension of macrophages (−8.9° [95% CI, −13.3° to −4.6°] versus −14.0° [95% CI, −18.0° to −10.0°]; difference, −6.0° [95% CI, −11.8° to −0.2°]; *P*=0.044). The minimum lumen area (−0.3 [95% CI, −0.5 to −0.1] mm^2 versus −0.2 [95% CI, −0.4 to −0.1] mm^2; difference, 0.1 [−0.1 to 0.4] mm^2; *P*=0.387) did not obviously change during follow-up. In the placebo group, there were 23.2% patients with OCT-derived TCFAs at baseline and 13.0% patients with TCFAs at follow-up. In the colchicine group, there were 21.0% patients with TCFAs at baseline and 8.4% patients with TCFAs at follow-up. The difference in change of TCFAs between the placebo and colchicine group was not significant from baseline to follow-up (odds ratio, 0.8 [95% CI, 0.5 to 1.3]; *P*=0.367; Table 2).

The analysis of exploratory OCT imaging parameters (lesion length, area stenosis, macrophage incidence, macrophages index, calcium incidence, microchannel incidence, and cholesterol crystals incidence) is also shown in Table 2. Among these parameters, there were no significant differences between the 2 groups from baseline to follow-up.

Although underpowered by sample size, the subgroups analysis of the absolute value change in minimal FCT is shown in Table 3. For subgroups of time from ACS to randomization, age, sex, current smoking, and previous

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Table 1. Baseline Clinical Characteristics

	Placebo (n=64)	Colchicine (n=64)
Age, y	60.3±8.5	55.7±10.6
<65	40 (62.5%)	50 (78.1%)
≥65	24 (37.5%)	14 (21.9%)
Sex (male/female)	48/16	48/16
Risk factors		
Current smoking	25 (39.1%)	25 (39.1%)
Body mass index, kg/m^2	24.4±3.1	24.4±3.3
Hypertension	44 (68.8%)	36 (56.3%)
Diabetes	16 (25.0%)	16 (25.0%)
Dyslipidemia	23 (35.9%)	33 (51.6%)
Peripheral arterial disease	3 (4.7%)	7 (10.9%)
Family history of CHD	8 (12.5%)	6 (9.4%)
Previous history		
Previous CHD	23 (35.9%)	17 (26.6%)
Previous PCI	5 (7.8%)	9 (14.1%)
Previous stroke	2 (3.1%)	1 (1.6%)
Heart failure	3 (4.7%)	1 (1.6%)
Chronic kidney disease	4 (6.3%)	3 (4.7%)
Estimated glomerular filtration rate, ml/(min·1.73m^2)	88.4±16.4	94.8±19.0
Type of ACS		
STEMI	2 (3.1%)	3 (4.7%)
NSTEMI	16 (25.0%)	18 (28.1%)
Unstable angina	46 (71.9%)	43 (67.2%)
Time from ACS to randomization, d acs	13.1±8.3	11.1±6.9
0–3 d	4 (6.3%)	4 (6.3%)
4–7 d	21 (32.8%)	20 (31.3%)
≥8 d	39 (60.9%)	40 (62.5%)
PCI performed		
Drug-eluting stent	62 (96.9%)	61 (95.3%)
Drug-coated balloon	2 (3.1%)	3 (4.7%)
Multivessel disease	13 (20.3%)	22 (34.4%)
No. of stents	1.9±1.0	2.1±1.3
Stent total length, mm	52.4±29.2	53.4±33.3
Stent average diameter, mm	3.0±0.7	3.4±2.2
Treatment		
Aspirin/indobufen	62 (96.9%)	64 (100%)
Clopidogrel/ticagrelor	64 (100%)	64 (100%)
Statin	62 (96.9%)	60 (93.8%)
β-Blocker	48 (75.0%)	48 (75.0%)
ACEI/ARB/ARNI	54 (84.4%)	49 (76.6%)
Ezetimibe	27 (42.2%)	29 (45.3%)
Statin+ezetimibe	26 (40.6%)	26 (40.6%)
PCSK9i	8 (12.5%)	11 (17.2%)
OCT target vessel		
Vessel numbers	95	110
Vessel position		
Left anterior descending artery	27 (28.4%)	27 (24.5%)
Left circumflex artery	34 (35.8%)	37 (33.6%)
Right coronary artery	34 (35.8%)	46 (41.8%)
Vessel properties		
Culprit vessel	18 (18.9%)	32 (29.1%)
Nonculprit vessel	77 (81.1%)	78 (70.9%)
OCT target plaque		
Plaque numbers	138	167
Diameter stenosis percentage, %	40.0±10.7	40.9±10.3

Normally distributed continuous variables are expressed as the mean±SD. Categorical variables are described as n (%). The estimated glomerular filtration rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. ACEI/ARB/ARNI indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor; ACS, acute coronary syndrome; CHD, coronary heart disease; NSTEMI, non–ST-segment–elevation myocardial infarction; OCT, optical coherence tomography; PCSK9i, proprotein convertase subtilisin/kexin-9 inhibitor; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

statin use, there was no statistical evidence of interaction. However, the absolute value change of minimal FCT in patients with baseline LDL-C (low-density lipoprotein cholesterol) ≤70 mg/dL was greater than that in patients with baseline LDL-C>70 mg/dL ($P_{interaction}$=0.027).

Biochemical and Inflammatory Biomarkers

The results of biochemical and inflammatory biomarkers were shown in Table 4 and Table 5, respectively. The baseline results of these indicators were not different between the placebo and colchicine groups. No significant changes in the triglycerides, fasting blood glucose, total cholesterol, LDL-C, apolipoprotein A1, apolipoprotein B, lipoprotein(a), or neutrophil-to-lymphocyte ratio levels were found during the follow-up period (Tables 4 and 5). Compared with placebo, colchicine treatment significantly reduced hsCRP (GMR, 0.6 [95% CI, 0.4 to 1.0] versus 0.3 [95% CI, 0.2 to 0.5]; difference, 0.5 [95% CI, 0.3 to 1.0]; *P*=0.046), IL-1 RA (GMR 1.0 [95% CI, 0.9 to 1.2] versus 0.7 [95% CI, 0.6 to 0.9]; difference, 0.7 [95% CI, 0.6 to 0.9]; *P*=0.003), IL-18 (GMR 1.0 [95% CI, 0.8 to 1.3] versus 0.6 [95% CI, 0.4 to 0.7]; difference, 0.6 [95% CI, 0.4 to 0.8]; *P*=0.001), IL-6 (GMR, 0.8 [95% CI, 0.6 to 1.1] versus 0.5 [95% CI, 0.4 to 0.7]; difference, 0.6 [95% CI, 0.4 to 0.9]; *P*=0.025), MPO (GMR, 1.0 [95% CI, 0.8 to 1.2] versus 0.8 [95% CI, 0.7 to 0.9]; difference, 0.8 [95% CI, 0.6 to 1.0]; *P*=0.047), and AZU1 (GMR, 0.9 [95% CI, 0.7 to 1.0] versus 0.6 [95% CI, 0.5 to 0.8]; difference, 0.7 [95% CI, 0.6 to 0.9]; *P*=0.019) levels from baseline to follow-up (Table 5).

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Table 2. OCT Findings at Baseline and Follow-Up

	Baseline		12-Mo follow-up		Change from baseline to 12 mo			
	Placebo (n=64)	Colchicine (n=64)	Placebo (n=52)	Colchicine (n=52)	Placebo (n=52)	Colchicine (n=52)	Difference in change	*P* value
Plaque numbers	138	167	108	131	108	131		
Primary end point								
Minimal fibrous cap thickness, μm*	130.9±70.2	139.6±76.0	185.4±90.6	227.8±124.4	51.9 (32.8 to 71.0)	87.2 (69.9 to 104.5)	34.2 (9.7 to 58.6)	0.006
Secondary end point								
Minimum lumen area, mm^2	5.1±2.5	4.5±2.3	4.5±2.3	4.2±2.4	−0.3 (−0.5 to −0.1)	−0.2 (−0.4 to −0.1)	0.1 (−0.1 to 0.4)	0.387
Average lipid arc, °	105.1±28.6	109.0±29.6	79.8±25.4	73.0±31.5	−25.2 (−30.6 to −19.9)	−35.7 (−40.5 to −30.8)	−10.5 (−17.7 to −3.4)	0.004
Mean macrophage angular extension, °	38.9±25.7	43.2±27.1	32.5±16.6	30.1±16.9	−8.9 (−13.3 to −4.6)	−14.0 (−18.0 to −10.0)	−6.0 −11.8 to −0.2)	0.044
Thin-cap fibroatheroma incidence, n (%)†	32 (23.2%)	35 (21.0%)	14 (13.0%)	11 (8.4%)	−10.2% (−19.4 to −1.1)	−12.6% (−4.6 to −20.5)	OR, 0.8 (0.5 to 1.3)	0.367
Exploratory end point								
Lesion length, mm	16.7±7.9	15.3±7.0	17.5±7.9	15.0±6.7	0.1 (−0.3 to 0.5)	−0.1 (−0.5 to 0.3)	−0.8 (−1.6 to 0)	0.054
Area stenosis, %	47.3±13.9	49.5±15.1	49.9±13.9	50.8±16.2	0.6 (−1.2 to 2.4)	0.6 (−1.1 to 2.2)	−0.8 (−3.3 to 1.7)	0.352
Minimal fibrous cap thickness categories								
<55 μm, n (%)	11 (8.0%)	10 (6.0%)	3 (2.8%)	3 (2.3%)	−5.2% (−10.3 to −0.1)	−3.7% (−7.3 to −0.1)	OR, 1.1 (0.2 to 5.9)	0.891
<65 μm, n (%)	31 (22.5%)	33 (19.8%)	8 (7.4%)	4 (3.1%)	−15.1% (−23.7 to −6.4)	−16.7% (−23.8 to −9.6)	OR, 0.5 (0.1 to 1.6)	0.228
<85 μm, n (%)	40 (29.0%)	50 (29.9%)	14 (13.0%)	8 (6.1%)	−16.0% (−25.5 to −6.5)	−23.8% (−31.9 to −15.8)	OR, 0.4 (0.2 to 1.0)	0.055
Macrophage incidence, n (%)	121 (87.7%)	149 (89.2%)	102 (94.4%)	119 (90.8%)	6.8% (−0.5 to 14.0)	1.6% (−2.8 to 6.1)	OR, 0.5 (0.2 to 1.3)	0.139
Macrophage index, mm	7.7±7.3	6.9±6.1	7.5±6.2	5.8±5.2	−1.1 (−2.0 to −0.1)	−1.3 (−2.1 to −0.4)	−0.5 (−1.7 to 0.8)	0.473
Calcium incidence, n (%)	53 (38.4%)	48 (28.7%)	52 (48.1%)	50 (38.2%)	9.7% (2.8 to 16.7)	9.4% (3.2 to 15.7)	OR, 0.9 (0.6 to 1.3)	0.732
Microchannel incidence, n (%)	82 (59.4%)	91 (54.5%)	72 (66.7%)	72 (55.0%)	7.2% (−1.5 to 16.0)	0.5% (−9.3 to 10.2)	OR, 0.7 (0.5 to 1.2)	0.197
Cholesterol crystals incidence, n (%)	95 (68.8%)	127 (76.0%)	79 (73.1%)	103 (78.6%)	4.3% (−7.4 to 16.0)	2.6% (−5.8 to 10.9)	OR, 1.0 (0.5 to 1.7)	0.863

OCT indicates optical coherence tomography; and OR, odds ratio.

*For normally distributed continuous variables (minimal fibrous cap thickness, etc), values are expressed as plaque-level mean±SD. The changes from baseline to 12-month are expressed as plaque-level mean absolute value change (95% CI). The analyses were conducted on plaque level values at 2 time points (baseline and 12-month follow-up) using linear mixed model accounting for the multiple plaques per patient, by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and plaque identity as the random effect. The differences in change were adjusted for age.

†For the categorical variable (thin-cap fibroatheroma incidence, etc), values are described as n (%). The analyses were conducted on plaque level values at 2 time points (baseline and 12-month follow-up) using generalized estimating equations for the multiple plaques per patient (plaque identity as subject variable, time point for baseline or 12-month follow-up as within-subject variable, binary logistic model, the interaction between group and time point as factor). The changes from baseline to 12-month are expressed as mean change (95% CI). The differences in change are expressed as OR with associated 95% CI adjusted for age.

Correlation Analysis

The correlations between the percentage changes from baseline to the 12-month follow-up of OCT parameters and biochemical/inflammatory biomarkers are shown in Figure 3. The percentage change of minimal FCT was negatively correlated with that of average lipid arc (r=−0.32; P=0.001). However, it was not correlated with the percentage of change in LDL-C, hsCRP, IL-6, or MPO.

The percentage change of average lipid arc was positively correlated with the percentage change of IL-6 (r=0.21; P=0.033) and MPO (r=0.21; P=0.031), but not correlated with that of LDL-C or hsCRP.

Clinical Outcomes and Adverse Events

The clinical end point consisting of a composite including all-cause death, nonfatal myocardial infarction, nonfatal

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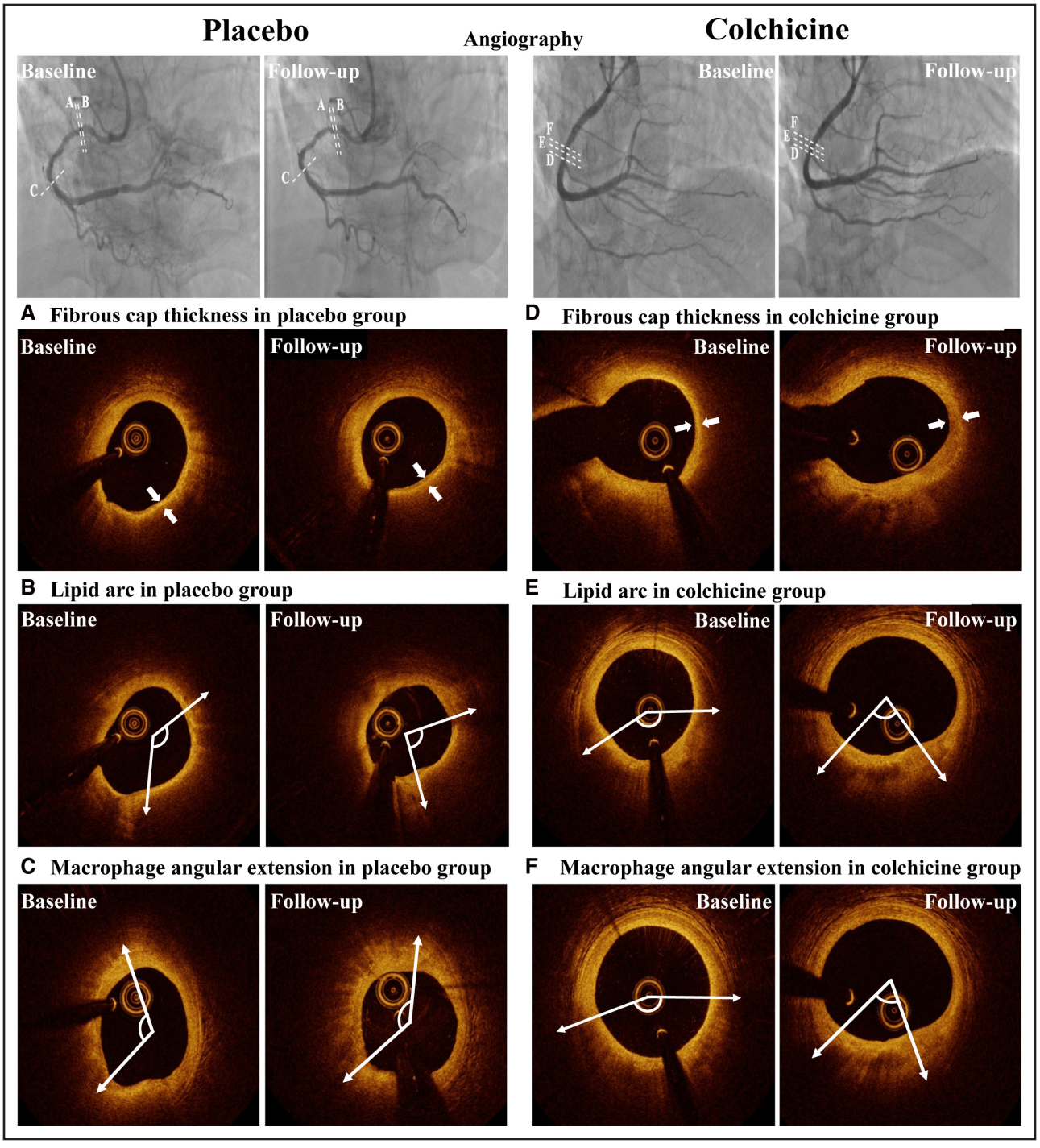

Figure 2. Representative picture of coronary artery plaque.
White dotted lines show the target lesion. The distance between white arrows indicates fibrous cap thickness; white lines indicate lipid arc and macrophage angular extension. **A**, Representative picture of fibrous cap thickness in placebo group. **B**, Representative picture of lipid arc in placebo group. **C**, Representative picture of macrophage angular extension in placebo group. **D**, Representative picture of fibrous cap thickness in colchicine group. **E**, Representative picture of lipid arc in colchicine group. **F**, Representative picture of macrophage angular extension in colchicine group.

stroke, and revascularization because of ischemia occurred in 17.3% of the participants in the placebo group and 11.5% of those in the colchicine group (*P*=0.402; Table S2).

A total of 128 patients (64 versus 64 in the placebo and colchicine groups, respectively) were included in the safety analysis set (Table S3). The frequencies of gastrointestinal symptoms with placebo versus colchicine were 6.3% versus 9.4% (*P*=0.744); for diarrhea, 1.6% versus 4.7% (*P*=0.619); for nausea, 1.6% versus 1.6% (*P*=1.000); and for flatulence, 3.1% versus 3.1% (*P*=1.000), respectively.

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Table 3. Primary End Point in Subgroups Analysis

	Baseline		12-Mo follow-up		Absolute value change of minimal fibrous cap thickness from baseline to 12 mo		Difference in change	*P* value	$P_{interaction}$
	Placebo (n=64)	Colchicine (n=64)	Placebo (n=52)	Colchicine (n=52)	Placebo (n=52)	Colchicine (n=52)			
Plaque numbers	138	167	108	131	108	131			
Time from acute coronary syndrome to randomization, d									
<8	25 (39.1%)	24 (37.5%)	20 (38.5%)	17 (32.7%)	40.3 (10.6 to 70.0)	102.8 (73.5 to 132.0)	63.7 (25.1 to 102.2)	0.001	0.141
≥8	39 (60.9%)	40 (62.5%)	32 (61.5%)	35 (67.3%)	58.0 (33.4 to 82.6)	80.8 (59.3 to 102.4)	22.0 (-9.5 to 53.5)	0.169	
Age, y									
<65	40 (62.5%)	50 (78.1%)	36 (69.2%)	42 (80.8%)	56.1 (33.2 to 79.1)	93.5 (73.7 to 113.4)	37.5 (8.5 to 66.6)	0.012	0.417
≥65	24 (37.5%)	14 (21.9%)	16 (30.8%)	10 (19.2%)	39.3 (7.4 to 71.3)	57.5 (22.9 to 92.1)	12.8 (–31.6 to 57.3)	0.565	
Sex									
Male	48 (75.0%)	48 (75.0%)	38 (73.1%)	38 (73.1%)	48.0 (27.0 to 69.0)	79.5 (60.2 to 98.8)	30.0 (3.0 to 56.9)	0.030	0.561
Female	16 (25.0%)	16 (25.0%)	14 (26.9%)	14 (26.9%)	66.7 (22.2 to 112.2)	113.0 (73.2 to 152.8)	47.9 (–10.3 to 106.1)	0.105	
Current smoking									
Yes	25 (39.1%)	25 (39.1%)	19 (36.5%)	21 (40.4%)	51.1 (21.6 to 80.6)	96.0 (70.1 to 122.0)	38.7 (1.3 to 76.0)	0.043	0.740
No	39 (60.9%)	39 (60.9%)	33 (63.5%)	31 (59.6%)	52.5 (27.1 to 77.9)	80.2 (56.6 to 103.8)	29.8 (–3.0 to 62.6)	0.075	
Previous statin use									
Yes	33 (51.6%)	26 (40.6%)	28 (53.8%)	22 (42.3%)	47.8 (20.2 to 75.3)	81.9 (54.4 to 109.4)	36.3 (–1.5 to 74.0)	0.059	0.836
No	31 (48.4%)	38 (59.4%)	24 (46.2%)	30 (57.7%)	55.3 (28.6 to 81.9)	90.3 (67.6 to 112.9)	30.7 (–1.8 to 63.3)	0.064	
Baseline LDL-C, mg/dL									
≤70	26 (40.6%)	19 (29.7%)	22 (42.3%)	15 (28.8%)	66.1 (33.9 to 98.2)	147.0 (104.2 to 189.8)	91.5 (41.7 to 141.3)	0.001	0.027
>70	38 (59.4%)	45 (70.3%)	30 (57.7%)	37 (71.2%)	41.5 (18.1 to 64.8)	72.4 (54.4 to 90.4)	26.2 (–1.9 to 54.3)	0.067	

The changes from baseline to 12 months are expressed as plaque-level mean absolute value change (95% CI). The analyses were conducted on plaque level values at 2 time points (baseline and 12-month follow-up) using linear mixed model accounting for the multiple plaques per patient, by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and plaque identity as the random effect. The differences in change were adjusted for age. For the categorical variable, values are described as n (%). LDL-C indicates low-density lipoprotein cholesterol.

Infection was reported as an adverse event in 6.3% of the participants in the placebo group, compared with 12.5% of those in the colchicine group (*P*=0.364).

DISCUSSION

In this study, we first clarified the effects of colchicine on coronary plaque characterization by OCT and yielded the following findings: (1) plaque stabilization was improved under the anti-inflammatory treatment with colchicine in patients with ACS, as evidenced by a greater increase in FCT, a decrease in the lipid arc, and reduced macrophage infiltration in OCT; (2) colchicine significantly reduced the levels of IL-RA/IL-18/IL-6/hsCRP and MPO/AZU1.

Dyslipidemia and inflammation jointly contribute to atherothrombotic disease. In contemporary practice, lipid-lowering therapies such as statin, ezetimibe, or PCSK9i (proprotein convertase subtilisin/kexin-9 inhibitors) therapy are currently recommended in almost all patients with CHD to reduce cardiovascular event risk.[24] Most guidelines for CHD have appropriately endorsed the concept that lower LDL-C is better worldwide. The plaque-stabilizing properties of lipid-lowering therapy have been evaluated by OCT in several studies.[16,17] As shown in a recent study, residual inflammatory risk was more strongly associated with future cardiovascular events than residual cholesterol risk.[25] However, it was unclear whether therapy targeting inflammatory risk could translate into

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Table 4. Biochemical Parameters at Baseline and Follow-Up

	Baseline		12-Mo follow-up		Absolute value change from baseline to 12 mo		Difference in change	*P* value
	Placebo (n=64)	Colchicine (n=64)	Placebo (n=52)	Colchicine (n=52)	Placebo (n=52)	Colchicine (n=52)		
TG, mg/dL*	101.8 (77.0, 138.1)	104.4 (77.9, 162.8)	97.3 (70.8, 141.6)	97.3 (79.6, 150.4)	0.9 (0.8 to 0.9)	0.9 (0.8 to 1.1)	1.0 (0.8 to 1.2)	0.624
FBG, mol/L	5.2 (4.8, 6.1)	5.1 (4.7, 5.6)	5.1 (4.7, 5.5)	4.8 (4.5, 5.7)	0.9 (0.8 to 1.0)	1 (0.9 to 1.1)	1.1 (0.9 to 1.2)	0.306
TC, mg/dL†	142.8±34.7	154.4±61.8	123.6±27.0	123.6±30.9	−19.8 (−32.5 to −7.1)	−38.9 (−51.5 to −26.2)	−10.8 (−30.5 to 8.9)	0.275
LDL-C, mg/dL	81.1±30.9	92.6±42.5	61.8±23.2	57.9±23.2	−20.4 (−30.3 to −10.4)	−37.3 (−47.2 to −27.3)	−12.0 (−26.6 to 2.7)	0.107
apo A1, mg/dL	120.1±18.4	122.4±19.3	138.0±18.1	142.0±19.8	17.3 (12.1 to 22.6)	17.9 (12.6 to 23.1)	1.0 (−6.1 to 8.2)	0.776
apoB, mg/dL	69.5±18.6	70.7±19.4	66.5±21.0	65.3±18.2	−4.0 (−9.9 to 2.0)	−4.4 (−10.2 to 1.6)	−1.9 (−10.3 to 6.6)	0.661
Lp(a), mg/dL	11.6 (6.4, 25.0)	16.3 (8.2, 25.3)	9.5 (5.0, 24.3)	12.9 (7.5, 20.5)	0.8 (0.7 to 0.9)	0.8 (0.7 to 1.0)	1.0 (0.8 to 1.2)	0.654

The analyses of linear mixed model were conducted on patient level values at 2 time points (baseline and 12-month follow-up) by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and patient identity as the random effect. To convert from mg/dL to mmol/L, multiply by 0.0259 for cholesterol, 0.0113 for triglyceride, and 0.01 for apolipoprotein. apo A1 indicates apolipoprotein A1; apoB, apolipoprotein B; FBG, fasting blood glucose; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglycerides.

*For nonnormally distributed continuous variables (TG, etc), values are expressed as median (first quartile, third quartile). The variables were log-transformed to achieve the normality for the analysis of linear mixed model. The changes from baseline to 12-month are expressed as geometric mean ratio (95% CI). The differences in change are expressed as geometric mean ratio (95% CI) adjusted for age.

†For normally distributed continuous variables (TC, etc), values are expressed as mean±SD. The changes from baseline to 12-month are expressed as mean absolute value change (95% CI). The differences in change were adjusted for age.

favorable plaque modification in ACS. Herein, we indicated that OCT parameters including FCT, lipid arc, and macrophage infiltration were improved under colchicine therapy in patients with ACS, which provided the direct evidence that anti-inflammatory therapy could induce plaque stabilization. For subgroups analysis, patients with baseline LDL-C≤70 mg/dL could benefit more significantly from plaque stability, which further indicated that targeting residual inflammation risk could be beneficial in patients with CHD with well-controlled LDL-C.

In the present study, the percentage change of minimum FCT in the placebo group was greater than the HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) and PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) studies.[17,26] This difference is mainly related to the lower LDL-C control during the follow-up period in the placebo group (61.8 mg/dL) compared with the HUYGENS (87.2 mg/dL) and PACMAN-AMI (74.4 mg/dL) studies (Table S4). The differences in population and risk profile might also result in the differences in the OCT parameter levels between this study and previous studies. Moreover, in this study, the percentage change of minimum FCT in

Table 5. Inflammatory Biomarkers at Baseline and Follow-Up

	Baseline		12-Mo follow-up		Absolute value change from baseline to 12 mo		Difference in change	*P* value
	Placebo (n=64)	Colchicine (n=64)	Placebo (n=52)	Colchicine (n=52)	Placebo (n=52)	Colchicine (n=52)		
hsCRP, mg/L	1.1 (0.4, 4.4)	1.2 (0.5, 5.6)	0.6 (0.2, 1.3)	0.5 (0.2, 1.3)	0.6 (0.4 to 1.0)	0.3 (0.2 to 0.5)	0.5 (0.3 to 1.0)	0.046
IL-1RA, pg/mL	95.3 (62.4, 143.7)	105.6 (75.9, 148.7)	91.9 (55.0, 168.5)	62.4 (42.6, 136.8)	1.0 (0.9 to 1.2)	0.7 (0.6 to 0.9)	0.7 (0.6 to 0.9)	0.003
IL-18, pg/mL	24.6 (14.4, 59.3)	26.1 (16.2, 40.5)	20.5 (11.5, 46.7)	14.5 (9.3, 20.2)	1.0 (0.8 to 1.3)	0.6 (0.4 to 0.7)	0.6 (0.4 to 0.8)	0.001
IL-6, pg/mL	5.8 (2.7, 17.2)	6.5 (3.0, 12.2)	4.5 (3.0, 11.5)	2.5 (2.1, 3.6)	0.8 (0.6 to 1.1)	0.5 (0.4 to 0.7)	0.6 (0.4 to 0.9)	0.025
NLR	2.4 (1.9, 3.4)	2.5 (1.8, 3.7)	2.2 (1.7, 2.9)	2.6 (1.7, 3.5)	0.9 (0.8 to 1.0)	1.0 (0.8 to 1.1)	1.1 (0.9 to 1.3)	0.362
MPO, ng/mL	2.9 (1.9, 3.7)	2.8 (2.0, 3.9)	2.7 (1.5, 3.9)	1.9 (1.3, 3.0)	1.0 (0.8 to 1.2)	0.8 (0.7 to 0.9)	0.8 (0.6 to 1.0)	0.047
AZU1, pg/mL	1.8 (1.5, 2.9)	2.0 (1.5, 2.8)	1.5 (1.2, 2.2)	1.2 (1.0, 1.7)	0.9 (0.7 to 1.0)	0.6 (0.5 to 0.8)	0.7 (0.6 to 0.9)	0.019

For nonnormally distributed continuous variables, values are expressed as median (first quartile, third quartile). The variables were log-transformed to achieve the normality for the analysis of linear mixed model. The changes from baseline to 12 months are expressed as geometric mean ratio (95% CI). The differences in change are expressed as geometric mean ratio (95% CI) adjusted for age. The analyses of linear mixed model were conducted on patient level values at 2 time points (baseline and 12-month follow-up) by fitting the interaction between group (placebo or colchicine) and time point (baseline or 12-month follow-up) as the fixed effect and patient identity as the random effect. AZU1 indicates azurocidin 1; hsCRP, high-sensitivity C-reactive protein; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-18, interleukin-18; MPO, myeloperoxidase; and NLR, neutrophil-to-lymphocyte ratio.

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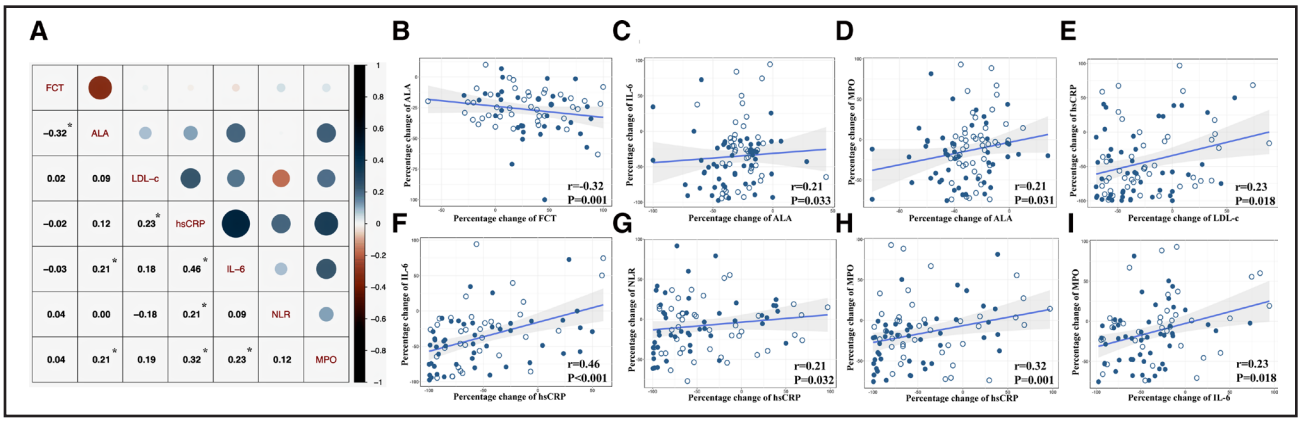

Figure 3. Correlations between the percentage changes from baseline to the 12-month follow-up of OCT parameters and biochemical/inflammatory biomarkers.

A, Spearman correlation heatmap analysis. *P<0.05. **B** through **I**, Scatter plots show the correlations between the percentage changes in the OCT parameters and biochemical/inflammatory biomarkers. Data exceeding the scale were not displayed. Hollow circle, placebo group; solid circle, colchicine group. ALA indicates average lipid arc; FCT, fibrous cap thickness; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MPO, myeloperoxidase; and NLR, neutrophil-to-lymphocyte ratio.

colchicine group was also greater than the previous studies of evolocumab and alirocumab.[17,26] From the perspective of clinical end point, evolocumab and alirocumab reduced the risk of major adverse cardiovascular and cerebrovascular events by 15%.[27,28] Colchicine reduced the risk of major adverse cardiovascular and cerebrovascular events by 23% in COLCOT.[8] Anti-inflammatory treatment with colchicine leads to a more significant reduction in the risk of major adverse cardiovascular and cerebrovascular events compared with the lipid-lowering treatment with PCSK9i, which is consistent with the more significant changes in minimum FCT caused by colchicine.

The favorable effects of colchicine on coronary plaque stability were found in the inhibition of inflammation. Recently, a few studies have explored several anti-inflammatory mechanisms potentially explaining the atheroprotective actions of colchicine including the inhibition of neutrophil activation, neutrophil-platelet interactions, and NLRP3 inflammasome assembly by the interference with microtubule function.[11] The anti-inflammatory mechanism of colchicine seems to vary depending on the different hsCRP levels. HsCRP is the indicator of NLRP3/IL-1β/IL-6 axis activation. In the patients with CHD with hsCRP>2 mg/L, the anti-inflammatory effect of colchicine has primarily focused on the NLRP3/IL-1β/IL-6 pathway.[13,29] During atherogenesis, activation of the NLRP3 inflammasome within plaque promotes the local generation of proinflammatory cytokines, which promote necrotic core formation by increasing cell death and accelerate fibrous cap thinning by degrading extracellular matrix macromolecules.[30–32]

Herein, the median of hsCRP level was 1.2 mg/L in the colchicine group, which was <2 mg/L. This was consistent with previous reports the hsCRP concentration had ethnic differences with especially lower levels in the East Asian populations.[33] It was reported that the neutrophil signaling implied an advantageous role for proinflammatory activation in patients with atherosclerosis with hsCRP≤2 mg/L in addition to the NLRP3/IL-1β/IL-6 pathway.[34] Neutrophil-driven proinflammatory responses could cause an inflammatory environment that promotes plaque destabilization and triggers thrombus formation.[35] The LoDoCo2 substudy indicated that neutrophil activation were obviously downregulated after colchicine treatment in the patients with CHD with hsCRP≤2 mg/L (median hsCRP level, 1.52 mg/L).[36] In this study, we also found a significant reduction in neutrophil activation (MPO/AZU1) besides NLRP3 inflammasome activation (IL-1RA/IL-18/IL-6/hsCRP) after colchicine treatment in patients with ACS. The correlation analysis between the changes in OCT parameters and inflammatory biomarkers further clarified this point of view. We showed that the changes in IL-6 and MPO were positively correlated with the percentage change in the average lipid arc after colchicine administration. Collectively, the potential anti-inflammatory mechanisms of colchicine seemed to be diverse, mainly targeting both neutrophil and NLRP3 inflammasome pathways. In addition, we found that the change of IL-6 was correlated with plaque stability. It indicated that IL-6 might be a suitable biomarker in vascular inflammation, as suggested by the subanalysis of CANTOS.[37]

Taken together, the findings show that anti-inflammatory therapy is one of the most promising strategies for combating residual cardiovascular risk. Although the favorable effects of colchicine on ACS were recommended in current guidelines based on the COLCOT study,[38] the mechanisms remain ill-defined. The increased risk of recurrent atherothrombotic events is mainly attributable to the progression of nonculprit lesions in ACS.[39,40] PCI is an important treatment for ACS, but plaque burden and unstability in the nonculprit lesion are significantly aggravated after PCI because of the stenting-triggered inflammation.[41] Thin fibrous cap and macrophage infiltration are the important discriminators of the high-risk unstable plaque, which lead to the increased risk for

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recurrent adverse cardiac events after ACS.[42,43] Our findings first revealed that colchicine favorably modified nonculprit plaque by increasing the FCT and alleviating macrophage infiltration through its anti-inflammatory effect, which provided the mechanistic rationale in favor of colchicine reducing recurrent atherothrombotic events in ACS, and were helpful for the interpretation of the COLCOT study. For culprit plaques, fibrous cap rupture and erosion are the 2 leading mechanisms that induce ACS, and the effect of colchicine on different culprit lesion phenotypes should be further explored. In addition, the strategy of drug-coated balloons would allow antiproliferative drug delivery to vulnerable plaques and medical therapy to be active in favoring plaque regression. The impact of oral colchicine therapy on 2 different PCI strategies (drug-coated balloons or drug-eluting stents) needs further exploration.

The proportion of unstable angina among patients with ACS was relatively high in this study compared with the typically observed rates in Europe.[44] One possible reason was that the proportion of unstable angina among ACS was higher in China.[45] Another possible cause was that certain patients with acute myocardial infarction could not tolerate prolonged OCT detection of all the 3 main epicardial coronary arteries. For patient safety reasons, these patients with acute myocardial infarction were not enrolled. In addition, some patients with acute myocardial infarction only underwent the revascularization of the culprit lesion during hospitalization, and they were excluded because of incomplete revascularization according to the inclusion criteria.

Limitations

This study was limited by its relatively small sample size, and the correlation between the percentage change in FCT and inflammatory biomarkers could not be reflected. This single-center study used a simple randomization method without stratification of confounding factors. Further evidence from randomized multicenter trials is needed. Biochemical and inflammatory biomarkers were detected only at baseline and at the 12-month follow-up, and the dynamic changes in these indicators were not well documented with colchicine therapy. The primary end point of this study was the change in the minimal FCT, and the sample size calculated based on the primary end point was insufficient to reflect the effect of colchicine on reducing clinical end points in the COLCOT study.

CONCLUSIONS

Our findings suggested colchicine improved coronary plaque stability as assessed by OCT, which could explain the underlying mechanism for the beneficial effect of colchicine treatment in patients with ACS.

ARTICLE INFORMATION

Received March 26, 2024; accepted July 16, 2024.

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Sources of Funding

This work was supported by grants from the National Key Research and Development Program (2022YFC2503501 and 2021YFC2500500), Chinese Society of Cardiology's Foundation (HFCSC2019B02 and CSCF2023A04), National Natural Science Foundation of China (82030016 and 82230011), and Hubei Natural Science Foundation (2020CFA020) to X.C.

Disclosures

None.

Supplemental Material

Tables S1–S4

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. *Circulation*. 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
3. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*. 1999;340:115–126. doi: 10.1056/NEJM199901143400207
4. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874. doi: 10.1038/nature01323
5. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. *Cardiovasc Res*. 2021;117:2525–2536. doi: 10.1093/cvr/cvab303
6. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM. Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J*. 2021;42:113–131. doi: 10.1093/eurheartj/ehaa099
7. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
8. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497–2505. doi: 10.1056/NEJMoa1912388
9. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383:1838–1847. doi: 10.1056/NEJMoa2021372
10. Nelson K, Fuster V, Ridker PM. Low-dose colchicine for secondary prevention of coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol*. 2023;82:648–660. doi: 10.1016/j.jacc.2023.05.055
11. Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J*. 2021;42:2745–2760. doi: 10.1093/eurheartj/ehab221
12. Bonaventura A, Abbate A. Colchicine for cardiovascular prevention: the dawn of a new era has finally come. *Eur Heart J*. 2023;44:3303–3304. doi: 10.1093/eurheartj/ehad453
13. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, Celermajer DS, Patel S. Colchicine therapy and plaque stabilization in patients with

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acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imaging*. 2018;11:305–316. doi: 10.1016/j.jcmg.2017.08.013
14. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J*. 2021;42:4671–4679. doi: 10.1093/eurheartj/ehab433
15. Xing L, Higuma T, Wang Z, Aguirre AD, Mizuno K, Takano M, Dauerman HL, Park SJ, Jang Y, Kim CJ, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: a 4-year follow-up study. *J Am Coll Cardiol*. 2017;69:2502–2513. doi: 10.1016/j.jacc.2017.03.556
16. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, Okumoto Y, Shiono Y, Orii M, Shimamura K, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. *J Am Coll Cardiol*. 2014;64:2207–2217. doi: 10.1016/j.jacc.2014.08.045
17. Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, Fahrni G, Iglesias JF, van Geuns RJ, Ondracek AS, et al; PACMAN-AMI collaborators. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA*. 2022;327:1771–1781. doi: 10.1001/jama.2022.5218
18. Juszczak E, Altman DG, Hopewell S, Schulz K. Reporting of multi-arm parallel-group randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2019;321:1610–1620. doi: 10.1001/jama.2019.3087
19. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, et al; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358
20. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, et al; Expert's OCT Review Document. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J*. 2010;31:401–415. doi: 10.1093/eurheartj/ehp433
21. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, et al; International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT). Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol*. 2012;59:1058–1072. doi: 10.1016/j.jacc.2011.09.079
22. Araki M, Park SJ, Dauerman HL, Uemura S, Kim JS, Di Mario C, Johnson TW, Guagliumi G, Kastrati A, Joner M, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nat Rev Cardiol*. 2022;19:684–703. doi: 10.1038/s41569-022-00687-9
23. Habara M, Nasu K, Terashima M, Ko E, Yokota D, Ito T, Kurita T, Teramoto T, Kimura M, Kinoshita Y, et al. Impact on optical coherence tomographic coronary findings of fluvastatin alone versus fluvastatin + ezetimibe. *Am J Cardiol*. 2014;113:580–587. doi: 10.1016/j.amjcard.2013.10.038
24. Tokgözoğlu L, Libby P. The dawn of a new era of targeted lipid-lowering therapies. *Eur Heart J*. 2022;43:3198–3208. doi: 10.1093/eurheartj/ehab841
25. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE; PROMINENT, REDUCE-IT, and STRENGTH Investigators. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet*. 2023;401:1293–1301. doi: 10.1016/S0140-6736(23)00215-5
26. Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T, Aradi D, Herrman JR, Hermanides RS, et al. Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. *JACC Cardiovasc Imaging*. 2022;15:1308–1321. doi: 10.1016/j.jcmg.2022.03.002
27. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664
28. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174
29. Robertson S, Martínez GJ, Payet CA, Barraclough JY, Celermajer DS, Bursill C, Patel S. Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP3 inflammasome monocyte activation. *Clin Sci (Lond)*. 2016;130:1237–1246. doi: 10.1042/CS20160090
30. Feig JE, Hewing B, Smith JD, Hazen SL, Fisher EA. High-density lipoprotein and atherosclerosis regression: evidence from preclinical and clinical studies. *Circ Res*. 2014;114:205–213. doi: 10.1161/CIRCRESAHA.114.300760
31. Dawson LP, Lum M, Nerleker N, Nicholls SJ, Layland J. Coronary atherosclerotic plaque regression: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79:66–82. doi: 10.1016/j.jacc.2021.10.035
32. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med*. 2013;368:2004–2013. doi: 10.1056/NEJMra1216063
33. Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, Matthews KA, Johnston J, Sowers MR, Sternfeld B, Pasternak RC, Chae CU; SWAN Investigators. Ethnic differences in C-reactive protein concentrations. *Clin Chem*. 2008;54:1027–1037. doi: 10.1373/clinchem.2007.098996
34. Nurmohamed NS, Belo Pereira JP, Hoogeveen RM, Kroon J, Kraaijenhof JM, Waissi F, Timmerman N, Bom MJ, Hoefer IE, Knaapen P, et al. Targeted proteomics improves cardiovascular risk prediction in secondary prevention. *Eur Heart J*. 2022;43:1569–1577. doi: 10.1093/eurheartj/ehac055
35. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. *Circ Res*. 2017;120:736–743. doi: 10.1161/CIRCRESAHA.116.309692
36. Opstal TSJ, Hoogeveen RM, Fiolet ATL, Silvis MJM, The SHK, Bax WA, de Kleijn DPV, Mosterd A, Stroes ESG, Cornel JH. Colchicine attenuates inflammation beyond the inflammasome in chronic coronary artery disease: a LoDoCo2 proteomic substudy. *Circulation*. 2020;142:1996–1998. doi: 10.1161/CIRCULATIONAHA.120.050560
37. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J*. 2018;39:3499–3507. doi: 10.1093/eurheartj/ehy310
38. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, et al; ESC Scientific Document Group. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720–3826. doi: 10.1093/eurheartj/ehad191
39. Scirica BM, Bergmark BA, Morrow DA, Antman EM, Bonaca MP, Murphy SA, Sabatine MS, Braunwald E, Wiviott SD. Nonculprit lesion myocardial infarction following percutaneous coronary intervention in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:1095–1106. doi: 10.1016/j.jacc.2019.12.067
40. Hong MK, Mintz GS, Lee CW, Kim YH, Lee SW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, et al. Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. *Circulation*. 2004;110:928–933. doi: 10.1161/01.CIR.0000139858.69915.2E
41. Ma J, Liu X, Qiao L, Meng L, Xu X, Xue F, Cheng C, Han Z, Lu Y, Zhang W, et al. Association between stent implantation and progression of non-target lesions in a rabbit model of atherosclerosis. *Circ Cardiovasc Interv*. 2021;14:e010764. doi: 10.1161/CIRCINTERVENTIONS.121.010764
42. Jiang S, Fang C, Xu X, Xing L, Sun S, Peng C, Yin Y, Lei F, Wang Y, Li L, et al. Identification of high-risk coronary lesions by 3-vessel optical coherence tomography. *J Am Coll Cardiol*. 2023;81:1217–1230. doi: 10.1016/j.jacc.2023.01.030
43. Montone RA, Vetrugno V, Camilli M, Russo M, Fracassi F, Khan SQ, Doshi SN, Townend JN, Ludman PF, Trani C, et al. Macrophage infiltrates in coronary plaque erosion and cardiovascular outcome in patients with acute coronary syndrome. *Atherosclerosis*. 2020;311:158–166. doi: 10.1016/j.atherosclerosis.2020.08.009
44. Bouisset F, Sia J, Mizukami T, Karjalainen PP, Tonino PAL, Pijls NHJ, Van der Heyden J, Romppanen H, Kervinen K, Airaksinen JKE, et al; TIDES-ACS Study Group. Titanium-nitride-oxide-coated vs everolimus-eluting stents in acute coronary syndrome: 5-year clinical outcomes of the TIDES-ACS randomized clinical trial. *JAMA Cardiol*. 2023;8:703–708. doi: 10.1001/jamacardio.2023.1373
45. Ge Z, Kan J, Gao X, Raza A, Zhang JJ, Mohydin BS, Gao F, Shao Y, Wang Y, Zeng H, et al. Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomized, placebo-controlled, double-blind clinical trial. *Lancet*. 2024;403:1866–1878. doi: 10.1016/s0140-6736(24)00473-2

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